REMARKS

Claims 14-18, 20-24, 26-28 are pending in the application; claims 19 and 25 have been canceled; claim 28 has been added.

Claim Rejections - 35 U.S.C. 112, 2nd Paragraph

Claims 14 to 27 stand rejected under 35 U.S.C. 112, 2nd paragraph, as being idenfinite.

Claims 14, 20, 21 are indefinite because of the phrase "preferably ...". This wording has been removed from the claims in question. Please note that in claim 14 the following errors have been corrected:

a) $\mathbf{(CH_3)_m}$-$(OCR^3HCH_2)_n$-$(O)_o$- has been corrected to read $\mathbf{(CH_2)_m}$-$(OCR^3HCH_2)_n$-$(O)_o$-;

b) $\mathbf{(CH_3)_q}$-$(OCR^5HCH_2)_r$-$(O)_s$-$(CH_3)_t$- has been corrected to read $\mathbf{(CH_2)_q}$-$(OCR^5HCH_2)_r$-$(O)_s$-$(CH_3)_t$

Claim 18 stands rejected because "therapeutic cancer agents, virustatic agents, anrtibiotics, ..." are set forth without being specific as to particular embodiments. It is respectfully submitted that the claim is belived to be definite as is. A person skilled in the art knows what the terms therapeutic cancer agent, virustatic agent, antibiotic, antimycotic agent, anti-inflammatory agent, substance that stimulates bone tissue or suppresses bone tissue mean. in addition, specific examples are listed in the specifcation (page 7, 4th paragraph, to page 8, 4th paragraph). The specification and not the claims of an application for patent are provided in order to render a detailed description and disclosure of the invention. In regard to claims and their contents, **MPEP 2173.02 Clarity and Precision** sets forth that

> "The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of

skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent....

The instant claims set forth certain types of agents (i.e. antibiotics, anti-inflammatory agents etc.) that apprise a person skilled in the art clearly of the scope of the claimed subject matter.

Also, it is standard practice to simply claim, for example, "antibiotic" and not a list of all possible antibiotics available. See in particular claim 2 of US 7,331,787 containing a list of agents similar to that of instant claim 18 (copies of front page and first claim page of US 7,331,787 are attached):

"2. The endodontic fiber of claim 1, wherein the medicament is selected from the group consisting of antibiotics, anti-inflammatory agents, antimicrobial agents, immune reagents, immunomodulatory agents, and combinations thereof."

Note that there are no specific antibiotics etc. listed in this claim; this is clear evidence that there is no requirement to incorporate a list of specifc antibiotics etc. into the claims for the claim to be definite.

Claim 19 has been canceled.

Claims 20, 21, 22, 26, 27 have been amended to set forth the derivatives.

Claim 27 has been reworded: the active agent or combination of active agents does not refer to the bisphosponic acids but to the substances as set forth in claim 17, for example.

In claim 23 the wording "in their natural, semi-synthetic..." has been deleted.

Reconsideration and withdrawal of the rejection of the claims 14-27 under 35 USC 112, 2nd paragraph, are respectfully requested.

Claim Rejections - 35 U.S.C. 112, 1st Paragraph

Claim 25 stands rejected under 35 USC 112, 1st paragraph, because the specification does not provide enablement for treating human diseases ansd animal diseases.

Claim 25 has been canceled and instead claim 28 directed to a liposomal composition has been added. The liposomal composition according to claim 21 comprises agents such as therapeutic cancer agents, virustatic agents, antibiotics, antimycotic agents, anti-inflammatory agents, substances that stimulates bone tissue or suppress bone tissue.

ALLOWABLE SUBJECT MATTER

No prior art has been applied against the claims. It appears that the claims are allowable.

CONCLUSION

In view of the foregoing, it is submitted that this application is now in condition for allowance and such allowance is respectfully solicited.

Should the Examiner have any further objections or suggestions, the undersigned would appreciate a phone call or **e-mail** from the examiner to discuss appropriate amendments to place the application into condition for allowance.

Authorization is herewith given to charge any fees or any shortages in any fees required during prosecution of this application and not paid by other means to Patent and Trademark Office deposit account 50-1199.

Respectfully submitted on May 26, 2008,

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GEH
Copies of US 7,331,787 (2 pages)

US007331787B2

(12) **United States Patent**
Abdennour et al.

(10) **Patent No.: US 7,331,787 B2**
(45) **Date of Patent: *Feb. 19, 2008**

(54) **CHARACTERIZATION OF AN ANTIBIOTIC IMPREGNATED DELIVERY SYSTEM AS AN INTRACANAL MEDICAMENT IN ENDODONTIC THERAPY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/812,638**

(22) Filed: **Mar. 29, 2004**

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Related U.S. Application Data

(63) Continuation of application No. 09/963,880, filed on Sep. 26, 2001, now Pat. No. 6,712,610, and a continuation-in-part of application No. 09/540,088, filed on Mar. 31, 2000, now abandoned.

(60) Provisional application No. 60/240,004, filed on Oct. 12, 2000, provisional application No. 60/127,497, filed on Apr. 2, 1999.

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
A61C 5/02 (2006.01)

(52) **U.S. Cl.** **433/81**

(58) **Field of Classification Search** 433/80, 433/81, 102, 224
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,003,810 A * 1/1977 Hoyt et al. 525/60

(Continued)

FOREIGN PATENT DOCUMENTS

EP 0 140 766 A2 5/1985

(Continued)

OTHER PUBLICATIONS

Grossman, L.I., "Polyantibiotic Treatment of Pulpless Teeth," *The Journal of the American Dental Association*, 43(3):265-278 (1951).

(Continued)

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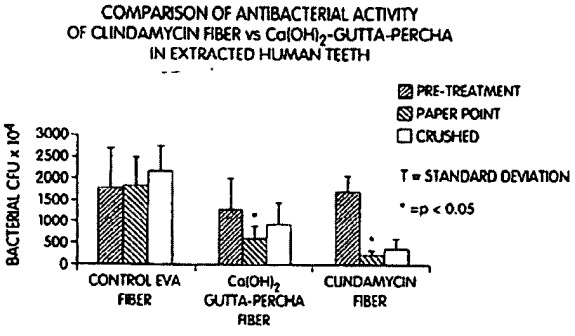
(57) **ABSTRACT**

Endodontic fibers comprising a biocompatible polymer vehicle permeable to medicaments, or combinations of medicaments are described. Such fibers can be used, for example, in a method for the local delivery and sustained release of medicaments to periodontal or intracanal treatment sites. Endodontic fibers described include modified periodontal fibers and intracanal fibers.

34 Claims, 10 Drawing Sheets



μL of *F. intermedia* and 100 μL of *S. intermedius* at a concentration of 10^8. The teeth were covered and placed in an anaerobic chamber for four days to allow for bacterial growth. Control fibers (EVA alone), calcium hydroxide/gutta-percha points or the intracanal clindamycin/EVA fibers were placed in each group of teeth. The teeth were replaced into fresh wells with 500 μL of sterile media, covered and incubated in the anaerobic chamber. The wells were replenished with sterile media every day until the next sampling (four days). The paper point samples were dispersed and vortexed in 1 mL of sterile PRAS transport medium under nitrogen influx. Ten-fold serial dilutions were performed by transferring 100 μL into 900 μL of (PRAS) under nitrogen influx for 10^{-2}, 10^{-3} and 10^{-4} dilutions. Finally, 100 μL samples were spread onto blood agar plates, and allowed to grow for five days under anaerobic conditions. The CPUs were quantified under light microscopy using a grid. Pour days after the placement of the delivery systems, the teeth were paper point sampled and assessed by serial dilution. To ensure that no bacterial were missed from complex anatomical spaces in the root canal system or from dentinal tubules, the teeth were individually fractured and crushed in sterile PRAS. Ten fold serial dilutions were performed as detailed above from the paper point samples and the crushed teeth samples. The CPUs from the diluted blood agar plates were quantified 7 days later. Statistical Analysis was determined between test groups in the in vitro model utilizing extracted human teeth using the ANOVA method and the Tukey's studentized range test. The ANOVA method revealed that there were no significant differences in infection levels at baseline prior to fiber placement (p=0.31134). However, after treatment both paper point and crushed experimental teeth treated with intracanal fibers has a statistically significant reduction in infection levels at 4 days post-treatment (p=0.0001) (FIGS. 7, 8, and 9) A statistically significant reduction was also noted for the $Ca(OH)_2$ gutta-percha group compared to the control group, although this was not as profound as the reduction by the intracanal fibers (FIG. 7). The intracanal fibers had the largest mean reduction (1515.8 CFUs), which is statisticall'significant from the $Ca(OH)_2$ gutta-percha group (701.6 CFUs) with ($p<0.05$). The Tukey's studentized range test also showed that the difference in post-treatment CFUs between the intracanal fiber group and the $Ca(OH)_2$ gutta-percha group was not statistically significant.

In vivo Suppression ofBacterial Growth in Auto-Infected Root Canals of Ferret 25 Canine Teeth by Intracanal Clindamycin/EVA Fibers

A similar protocol to the periodontal in vivo study detailed above was conducted. Briefly, teeth from six ferrets were utilized into four treatment groups. The groups were control/EVA fibers, clindamycin/EVA intracanal fibers, Roeko® fibers and calcium hydroxide paste.

The ferrets were infected with a mixture of four common endodontic pathogens, including *Streptococcus intermedius, Fusobacterium nucleatim, Peptostreptococcus micros*, and *Prevotella intermedia.*

To analyze the residual infection, paper point samples were taken, the teeth were extracted and then crushed to release all bacteria within the root canals. The results are shown in FIG. 10.

While this invention has been particularly shown and described with reference to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

What is claimed is:

1. An endodontic fiber suitable for the local delivery and sustained release of one or more medicaments incorporated therein to an intracanal treatment site, comprising a polymer vehicle having incorporated therein one or more medicaments, wherein said endodontic fiber is capable of being positioned deep within a root canal to enable said one or more medicaments to act locally at a site of deep bacterial infection and wherein said endodontic fiber comprises a dose of said one or more medicaments of about 2.0 mg to about 5.0 mg per 10 mm of fiber.

2. The endodontic fiber of claim 1, wherein the medicament is selected from the group consisting of antibiotics, anti-inflammatory agents, antimicrobial agents, immune reagents, immunomodulatory agents, and combinations thereof.

3. The endodontic fiber of claim 2, wherein the medicament is an antibiotic selected from the group consisting of clindamycin, tetracycline and combinations thereof.

4. The endodontic fiber of claim 2, wherein the medicament comprises a combination of an antibiotic and an anti-inflanunatory agent.

5. The endodontic fiber of claim 1, wherein the polymer vehicle is an ethylene vinyl acetate copolymer having a diameter of from about 0.1 mm to about 2.0 mm and the medicament is clindamycin incorporated at a dose of about 2.0 mg to about 5.0 mg per 10 mm of fiber.

6. The endodontic fiber of claim 1, wherein said polymer vehicle comprises an ethylene vinyl acetate copolymer comprising less than about 20% vinyl acetate by weight.

7. The endodontic fiber according to claim 6, comprising less than about 15% vinyl acetate by weight.

8. The endodontic fiber according to claim 6, comprising less than about 10% vinyl acetate by weight.

9. The endodontic fiber according to claim 6, comprising about 9.3% vinyl acetate by weight.

10. The endodontic fiber according to claim 9, having a diameter of less than about 0.5 mm and one or more medicament incorporated therein.

11. The endodontic fiber according to claim 6, having a diameter of less than about 0.5 mm.

12. The endodontic fiber of claim 6, wherein said fiber is impregnated with said one or more medicaments.

13. The endodontic fiber of claim 6, wherein said fiber has a rigidity similar to traditional gutta percha points.

14. The endodontic fiber of claim 1, wherein said fiber is impregnated with said one or more medicaments.

15. The endodontic fiber of claim 1, wherein said fiber has a rigidity similar to traditional gutta percha points.

16. A modified periodontal fiber suitable for the delivery and sustained release of one or more medicaments incorporated therein to an intracanal treatment site, comprising a polymer vehicle having incorporated therein one or more medicaments, wherein the polymer is treated to decrease its surface tackiness, wherein said endodontic fiber is capable of being positioned deep within a root canal to enable said one or more medicaments to act locally at a site of deep bacterial infection, and wherein said endodontic fiber comprises a dose of said one or more medicaments of about 2.0 mg to about 5.0 mg per 10 mm of fiber.

17. The modified periodontal fiber of claim 16, wherein said fiber is impregnated with said one or more medicaments.

18. The modified periodontal fiber of claim 6, wherein said fiber has a rigidity similar to traditional gutta percha points.